8 Conclusions and recommendations

After thorough discussions of the many initial options, the following major themes were proposed:

8.1 Treatment of CFA

Three interrelated research issues were addressed within the clinical theme.

8.1.1 Evidence-based care

This issue focuses on the replacement of current widespread uncertainty and confusion in clinical care with a sound evidence-base derived from rigorous clinical research.

There is a pressing need to mobilize a critical mass of clinical research expertise and to access sufficiently large samples of patients for adequately-powered clinical trials. Initial efforts should include the following:

- trials of surgical methods for the repair of different orofacial cleft subtypes, not just unilateral clefts;
- trials of surgical methods for the correction of velopharyngeal insufficiency;
- trials of the use of prophylactic ventilation tubes (grommets) for middle-ear disease in patients with cleft palate;
- trials of adjunctive procedures in cleft care, especially those that place an increased burden on the patient, family, or medical services, such as presurgical orthopaedics, primary dentition, orthodontics and maxillary protraction;
- trials of methods for the management of perioperature pain, swelling and infection, and nursing;
- trials of methods to optimize feeding before and after surgery;

- trials addressing the special circumstances of care in the developing world in respect of surgical, anaesthetic and nursing care;
- trials of different modalities of speech therapy, orthodontic treatment and counselling.

Equally urgent is the need to create collaborative groups, or improve the networking of existing groups, in order to develop and standardize outcome measures. There is an especially urgent need for work on psychological and quality-of-life measures, and economic outcomes.

For rare interventions, prospective registries should be established to hasten collaborative monitoring and critical appraisal, equivalent to Phase I trials. Relevant topics would be craniosynostosis surgery, ear reconstruction, distraction osteogenesis for hemifacial macrosomia and other skeletal variations, midface surgery in craniofacial dysostosis, and correction of hypertelorism.

8.1.2 Quality improvement

Quality improvement focuses on the development and dissemination of methodologies for monitoring and improving the delivery of clinical services.

The international adoption of a set guideline for the provision of clinical services and for the maintenance and analysis of minimum clinical records of cleft care is proposed. Various registries of clinical outcomes have recently emerged and are working independently. Efforts should be made to harmonize these.

8.1.3 Access and availability

Identify strategies to maximize access to adequate levels of care for all affected individuals, irrespective of nationality.

In large parts of the world, routine public health services are unable to afford treatment for CFA. Three general approaches can be identified: high volume indigenous centres of excellence; contracts between non-governmental organizations (NGOs) and local hospitals; and volunteer short-term surgical missions. The long-term benefit of these efforts could be developed by:

- a survey of the charitable organizations involved and the scale of their work;
- an appraisal of the cost-effectiveness and clinical effectiveness of the different models of aid;

- the promotion of dialogue between different NGOs to develop commonly-agreed codes of practice and adoption of the most appropriate forms of aid for local circumstances, with an emphasis on support that favours indigenous long-term solutions;
- the initiation of clinical trials concerning the specifics of surgery in a developing country setting, one-stage operations, optimal late primary surgery, anaesthesia protocols (e.g. local anaesthetic, inhalation sedation), antisepsis;
- the development of common core protocols for genetic, epidemiological and nutritional studies alongside surgery.

8.2 Gene/environment interaction

8.2.1 Epidemiology

The overall conclusions to be drawn from the data presented are as follows:

- there is ample evidence of the distinctly different nature of CL/P and CP, and emerging evidence of distinct differences in sub-groups within these overall conditions;
- there is a great deal of geographical variation which is more apparent for CL/P than CP;
- there is considerable variation in the proportion of cases of OFC with additional congenital anomalies and syndromes;
- it is evident that migrant groups retain rates of CL/P similar to those of their area of origin;
- there is no consistent evidence of time trends, nor is there consistent variation by socioeconomic status or seasonality, but neither of these aspects have been adequately studied;
- there is considerable international variation in the frequency of orofacial clefts, but validity and comparability of data are adversely affected by numerous factors, among which are:
  (a) source population of births considered (hospital versus population),
  (b) time period,
  (c) method of ascertainment,
  (d) inclusion/exclusion criteria, and
  (e) sampling fluctuation;
- there are many parts of the world where we have little or no information on the frequency of OFC, in particular parts of Africa, Central Asia, Eastern Europe, Middle East and Russia.

8.2.2 Etiology

The following points are relevant:

- there are multiple genes involved in OFC;
- analysis should be separated for CL, CL/P and CP as CL/P is not the same as CL only;
- heterogeneity should be expected and therefore different populations will need to be examined for validation of a result;
- nutrition remains an eligible area for research, and the roles of folic acid and multivitamins, including folic acid, vitamins A, B2, B6 and B12, as well as zinc, need further investigation;
- smoking, alcohol, epilepsy, certain medications and environmental factors may explain a small but appreciable portion of birth defects;
- main gaps in knowledge are examination of co-teratogens and gene/environment interaction e.g. with alcohol are there co-teratogens, such as folate deficiency, and is there a threshold beneath which alcohol is safe?

It is important to be able to differentiate the exposure and the genetic predisposition; and identify those at risk to allow selective counselling since general advice regarding alcohol and smoking in relation to disease is not easy to impart in attempting to achieve changes in behaviour.

One major issue in the reporting of associations with exposures is the distinct possibility of publication bias in the literature.

8.2.3 WHO aims and objectives for gene/environment interaction research

The ultimate humanitarian and scientific research objective in CFA birth defects is *primary prevention.*

The WHO project aims to:

- provide support for planning and development of research protocols that will advance understanding of etiology and inform future prevention initiatives;
- facilitate internet-based research databases;
- support gene/environment interaction studies with international standardization of research protocols to inform the design of future efforts towards primary prevention.

These objectives can be achieved by:

- the reinforcement of existing research collaborations, and
- the setting up of new research collaborations.

8.2.4 Future research challenges

With the availability of the human genome sequence, researchers have increasing opportunities to study the role of genes and GEI in human health and disease. Such opportunities come with major challenges, in three main areas:

- **The first area relates to data:** to identify and, if possible, rank the major data gaps separating our current knowledge from that needed for clinical and public health action.
- **The second area relates to methods:** how to conduct, analyse and present studies of multiple genetic and environmental factors in ways that efficiently fill the data gaps.
- **The third area relates to people and institutions:** how to learn more and more quickly using the unique opportunities inherent in international collaboration.

Common core protocols for data collection and further studies into research methodology to compare various data analysis models are urgently required.

8.3 Genetics

The focus of the genetics component of the WHO Craniofacial Conference was on discussing those technologies, analytic approaches and populations that will best move us forward towards a better understanding of the etiologies of craniofacial abnormalities with particular reference to those that have strong genetic components. While recognizing that the environment and stochastic events play an important and, often, major role in predisposing to craniofacial anomalies, in many situations the role of genetics is compelling.

8.3.1 Phenotype/genotype correlation

- A number of specific single-gene disorders with recognizable Mendelian inheritance, including some holoprosencephaly and craniosynostosis syndromes, serve as benchmarks for ways in which gene identification can proceed from clinical description and family-based studies through traditional cloning and functional analysis.

- The definition of non-syndromic cleft lip and palate remains ambiguous, and new gene discoveries leading to improvements in genetic diagnoses will potentially improve sensitivity and specificity of genotype/phenotype correlation.
- There is some emerging evidence that traditional separations between cleft lip, with or without cleft palate, and cleft palate only, may be breaking down, and further work in this area is essential.
- It is therefore important in research to be able to sub-phenotype cases of children whose abnormalities are limited to clefts, or clefts and one additional abnormality. Clinical descriptors that will allow breaking this group down into finer detail will be particularly important in facilitating genetic analysis.

8.3.2 Analytical methodologies

- Technological and analytic approaches will include new methodologies for genotyping, the strategy by which markers will be chosen for genotyping, and the selection of candidate genes when that approach is being utilized.
- The strengths and weaknesses of traditional linkage approaches versus affected pedigree-member approaches and transmission disequilibrium testing (TDT) and linkage disequilibrium were also developed.
- The strengths of these approaches often overlap and combinatorial approaches using candidate genes in conjunction with affected pedigree-member linkage and TDT can all be carried out in parallel with one another.

8.3.3 Collection and storage of genetic data

- Analysis is driven by sample collection, and there are both strengths and weaknesses in:
  (a) rapid, cost-efficient, and small-amount sample collection, as is exemplified by blood spots or cheek swabs; and
  (b) whole blood or cell line collections that would allow for more extensive analysis of protein and RNA.
- International collaboration is essential in that etiologies are likely to be diverse across populations but with some underlying gene and environmental causes shared in common.
- Multi-centre collaborations afford the opportunity for the collection of large numbers of samples to have sufficient power to confirm

linkage or association studies; there are a number of active on-going collaborations.

8.3.4 Parallel research and multidisciplinary approach

- The role of animal models and the insights gained from developmental biology into choosing both genes and pathways involved in CFA genetics have never been more apparent than they are now.
- It will be through the interactive efforts of clinicians, epidemiologists, statisticians, molecular biologists and developmental biologists that we will make our most rapid progress.

8.3.5 Role of the World Health Organization

In the ongoing efforts to globalize CFA research, the WHO group will coordinate work on outlining candidate genes, markers, analytic approaches and animal models of use, and will streamline efforts towards establishing collaborative groups to establish a set of protocols and guidelines for future efforts in this arena.

8.4 Prevention

8.4.1 Primary prevention

Orofacial clefts appear to have substantial environmental causes; the potential for their occurrence thus seems considerable. The pattern of occurrence of orofacial clefts is different from that of neural tube defects so their causes may also be different.

- **Maternal tobacco** use has been consistently associated with a modest elevation in risk of orofacial clefts but the attributable risk may be of public health importance. Moreover tobacco use is rapidly increasing among women, especially in technologically developing countries, and many women are exposed to passive smoking in the home and workplace.
- **Maternal alcohol** use, well known as a cause of the fetal alcohol syndrome, has also been associated with risk of isolated orofacial clefts in some, but not all, studies. The type and context of alcohol consumption differs considerably across populations and more consistent methods are needed for the assessment of maternal alcohol intake. The possible increased risk of orofacial clefts and other CFA related to the common exposures of smoking and alcohol use during pregnancy is a message that should be incorporated into health promotion programmes for women of reproductive age.

- **Maternal nutritional factors** have been associated with the risk for orofacial clefts in human population studies, although strong evidence of a causal relationship is still lacking. The most promising candidate nutrients include folic acid and pyridoxine (vitamin B-6) and some evidence also exists of possible roles for riboflavin (vitamin B-2) and vitamin A.

8.4.2 Intervention trials

The current state of equipoise regarding maternal nutrition and orofacial clefts makes intervention trials of specific nutrients an urgent priority. The proven intervention of folic acid supplements in the prevention of occurrence of NTDs must also be acknowledged in the design of prevention trials involving folic acid. No single trial is likely to be definitive and trials are needed in diverse populations in both industrialized and technologically developing countries. Trials in high-risk populations are more likely to detect a treatment effect than trials in low-risk populations, and at lower cost and with greater speed.

8.4.3 Choice of nutrient

The choice of specific nutrient interventions should be based on prior detailed studies of biochemical indicators of nutritional status in the population of interest, and all prevention trials should adhere to current ethical and methodologic standards. Poorly conceived and conducted trials are unethical because they waste limited resources and add further delay to discovering effective interventions.

8.4.4 Recurrence trial

An orofacial-cleft recurrence-prevention trial is far more feasible than a trial of prevention of primary occurrence, but would still require many thousands of high-risk mothers. Orofacial cleft surveillance systems and registries in countries around the world need to be further developed and linked to provide the critical infrastructure for orofacial-cleft prevention trials.